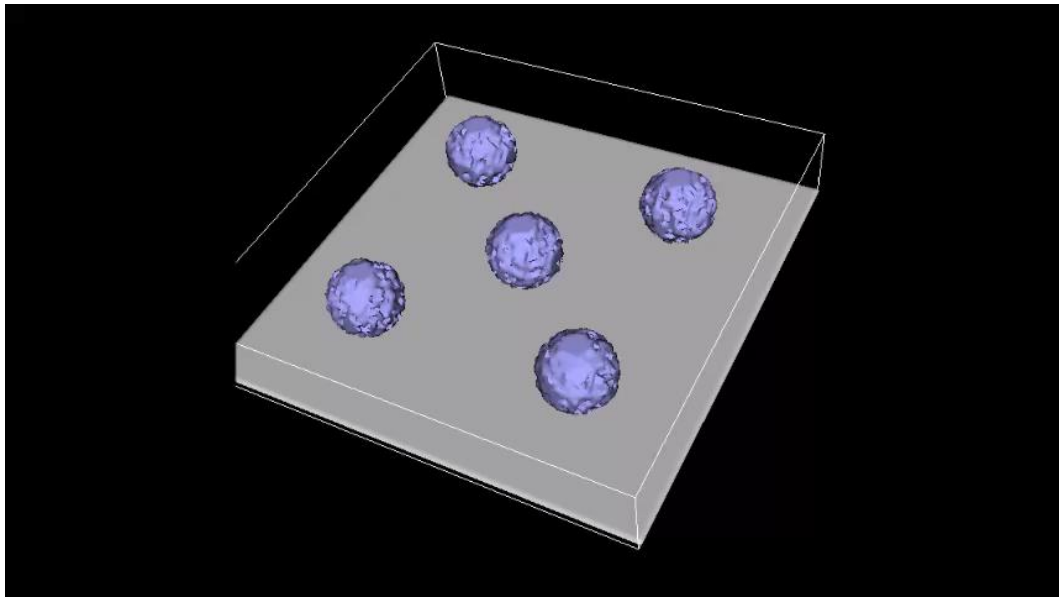
A Project!

Epithelial-Mesenchymal transformation, cell migration, and active solids.



Rita M.C.de Almeida

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PPG em Bioinformática – UFRN

INCT: Sistemas Complexos

Collaborators

- Gilberto L. Thomas
- Leonardo Brunnet
- Pedro dal Castel
- Guilherme Shoiti Giardini
- Luís Gustavo Gaiato
- Rodrigo Dalmolin
- Julio M. Belmonte
- James A. Glazier
- François Graner
- Ismael Fortuna
- Gabriel C. Perrone
- Mendeli Vainstein
- Carine Beatrici











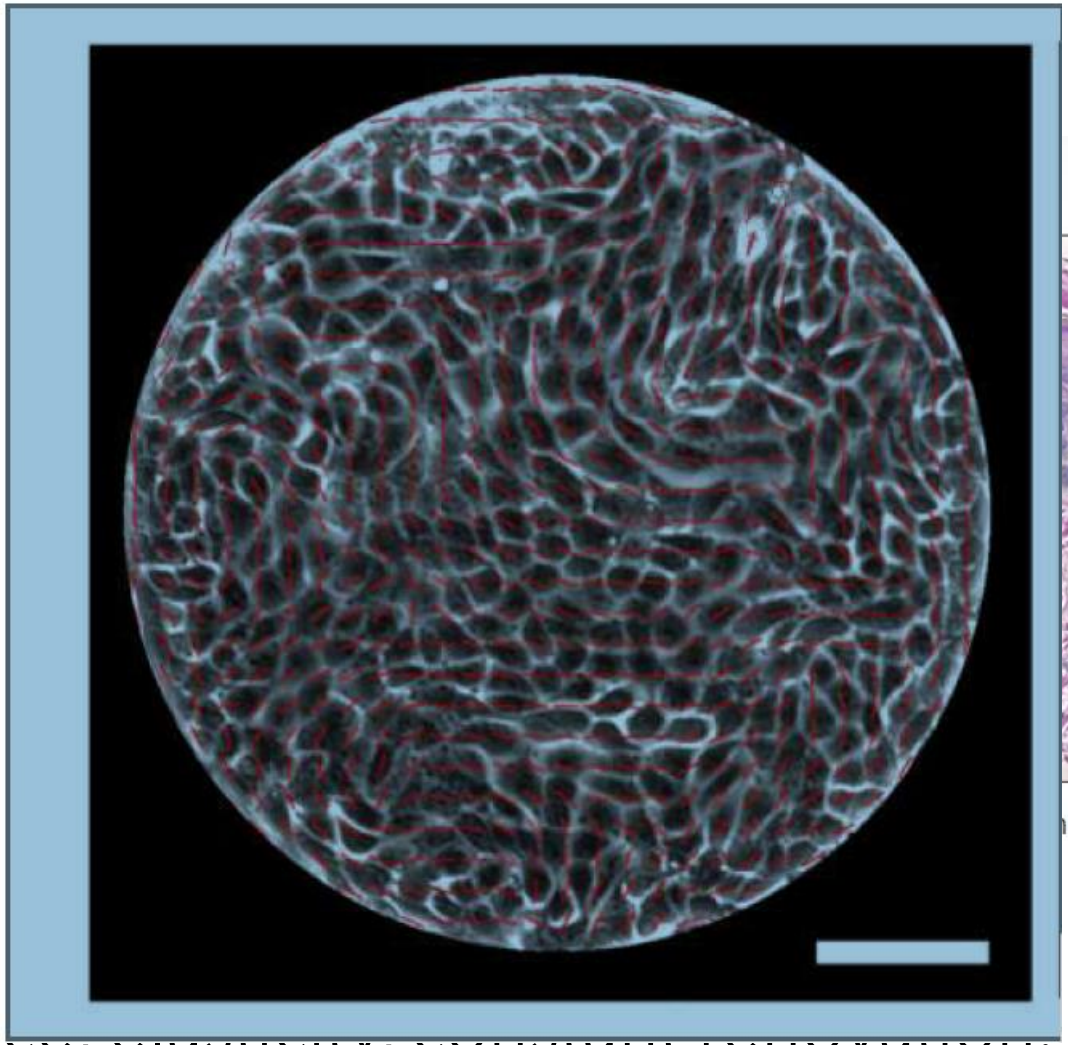

Epithelial –mesenchymal transformation (EMT)

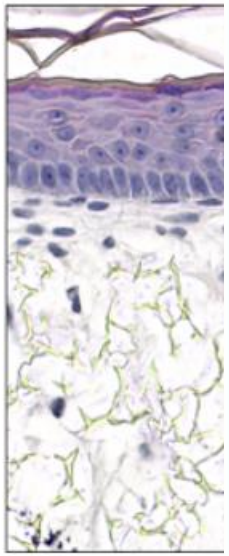
+ From epithelial to mesenchymal phenotype
+ MET (mesenchymal to epithelual)
+ Wound healing
+ Development
+ Metastases.

wound healing assay - Pesquisa Google

CNPq

CAPES





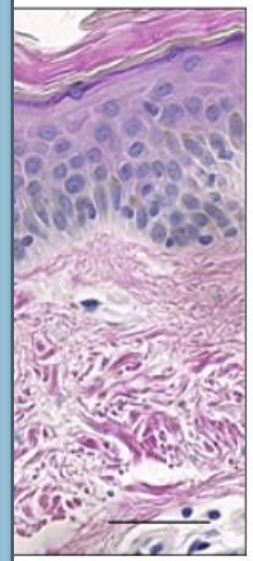


Figure 3. Human

to *in vivo* human

C

+

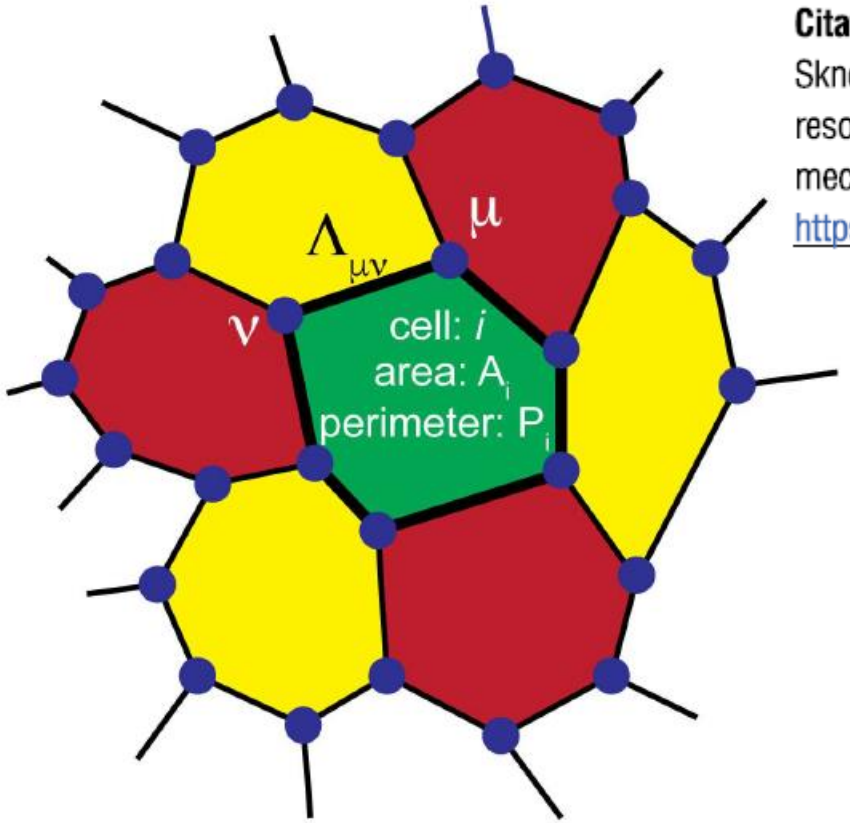
+

+

+ active sc

+ Resisten

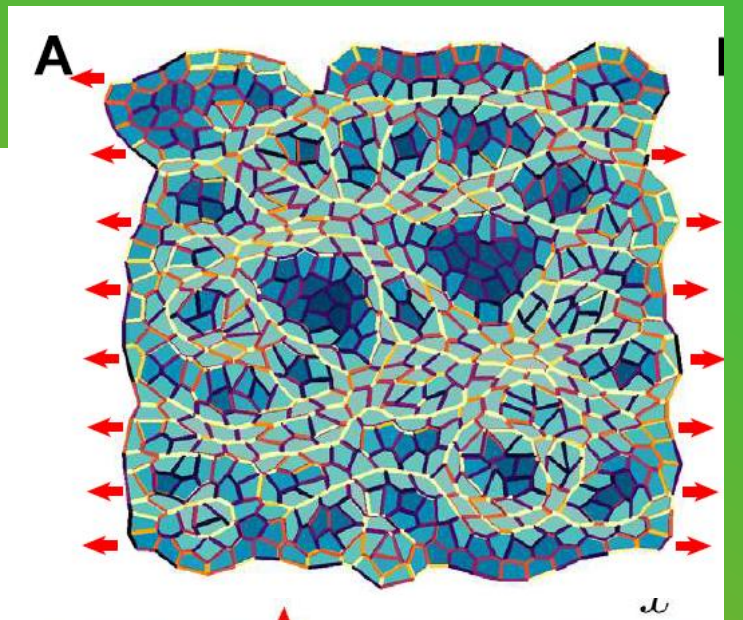
Vertex model

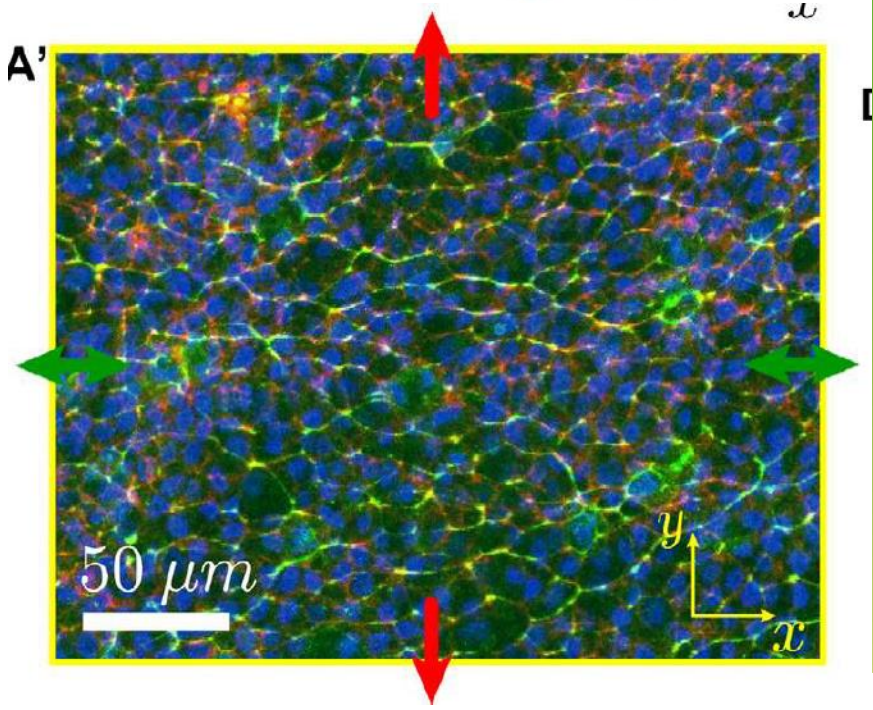


Citation: Barton DL, Henkes S, Weijer CJ, Sknepnek R (2017) Active Vertex Model for cell-resolution description of epithelial tissue mechanics. PLoS Comput Biol 13(6): e1005569. https://doi.org/10.1371/journal.pcbi.1005569

Fig 1. In the Vertex Model (VM), a confluent epithelial sheet is represented as a polygonal tiling of the plane with no holes or overlaps. Each cell is represented by an n–sided polygon. Neighbouring cells share an edge, which models the cell junction as a straight line. Three edges meet at a vertex (dark blue dots). The behaviour of cell i is described by three parameters: 1) reference area A_i^0, 2) area modulus K_i, and 3)

$$E_{VM} = \sum_{i=1}^{N} \frac{K_i}{2}\left(A_i - A_i^0\right)^2 + \sum_{i=1}^{N} \frac{\Gamma_i}{2} P_i^2 + 2\sum_{\langle\mu,\nu\rangle} \Lambda_{\mu\nu} l_{\mu\nu},$$





Sknepnek *et al.* eLife 2023;12:e79862.

Mesenchymal cells

+ Migration
+ Chemotaxis
+ Adhesion to matrix componentes (fibers)
+ Rear-front polarization.

https://www.google.com.br/search?q=wound+healing+assay&source=lmns&tbm=vid&hl=pt-BR&sa=X&ved=2ahUKEwjL-cWfgv6BAxWePrkGHdqSDJgQ_AUoAnoECAEQAg#fpstate=ive&vld=cid:e9b3e2b0,vid:OWC8pGMqza0,st:0

Zhou et al.
J Cell Sci (2020) 133 (17): jcs248880.

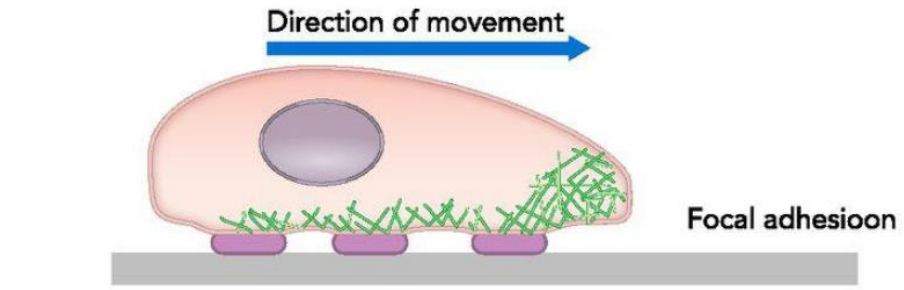
Maiuri,…, Voituriez,
Cell 161, 374–386, April 9, 2015

BMDC WT
2D + Confinement
30°C

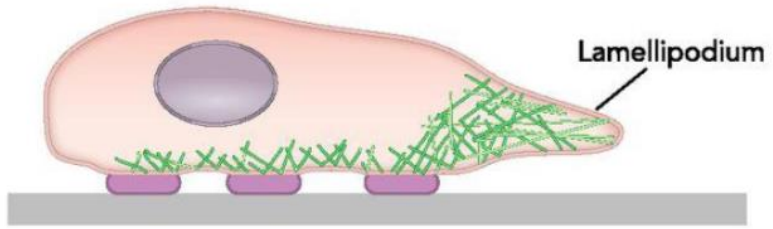
BMDC 2D + Confinement

Diffusive

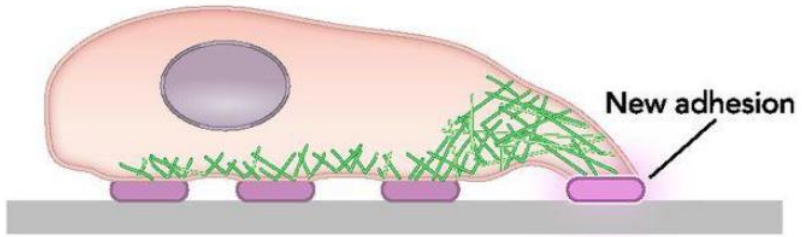
Abercrombie model



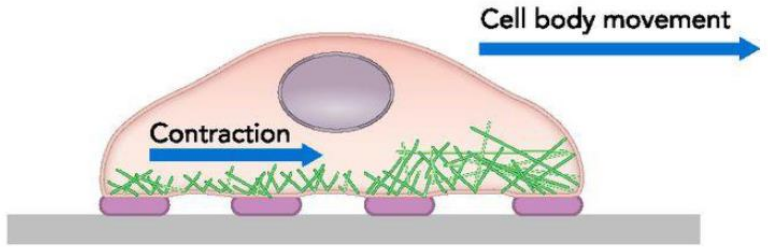
1. Extension



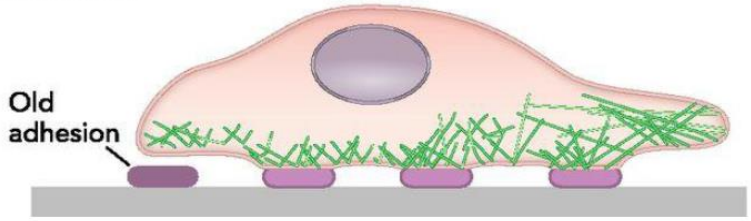
2. Adhesion



3. Translocation



4. De-adhesion



Abercrombie et al., Experimental cell research,1971

Fortuna, ..., RMCdeA, Biophysical Journal, 118, p 2801, 2020
https://doi.org/10.1016/j.bpj.2020.04.024

Design:

- 0 – Medium
- The Cell: 3 compartments
  1. Nucleus
  2. Cytoplasm
  3. Lamellipodium (Front)
- 4 – Substratum
- Actin cortex

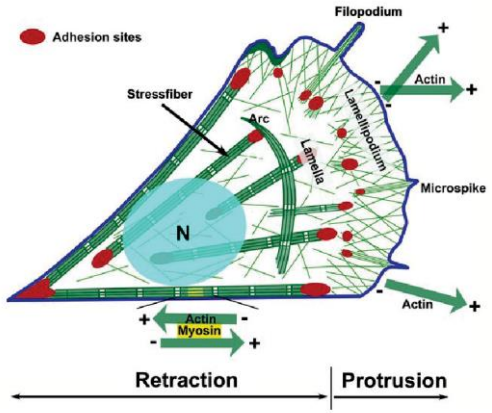
→ density fields (actin polymers represented by F-Actin)

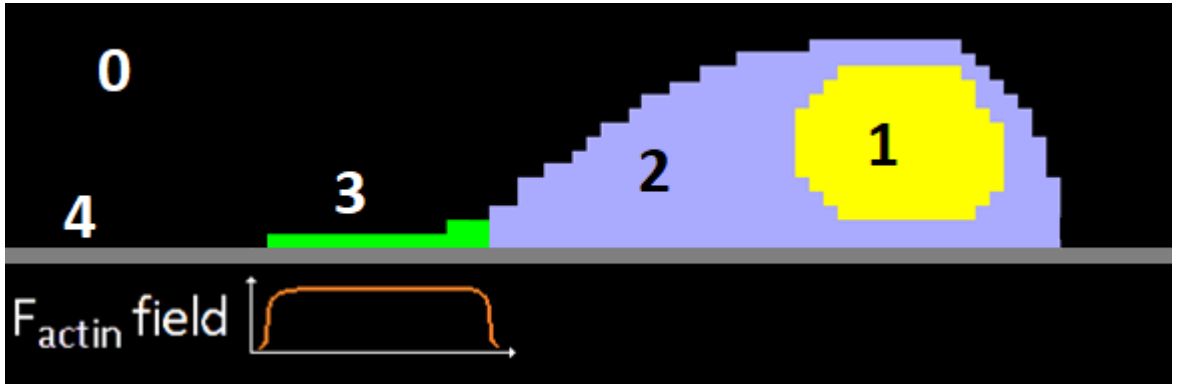
- No focal contacts

Dynamics:

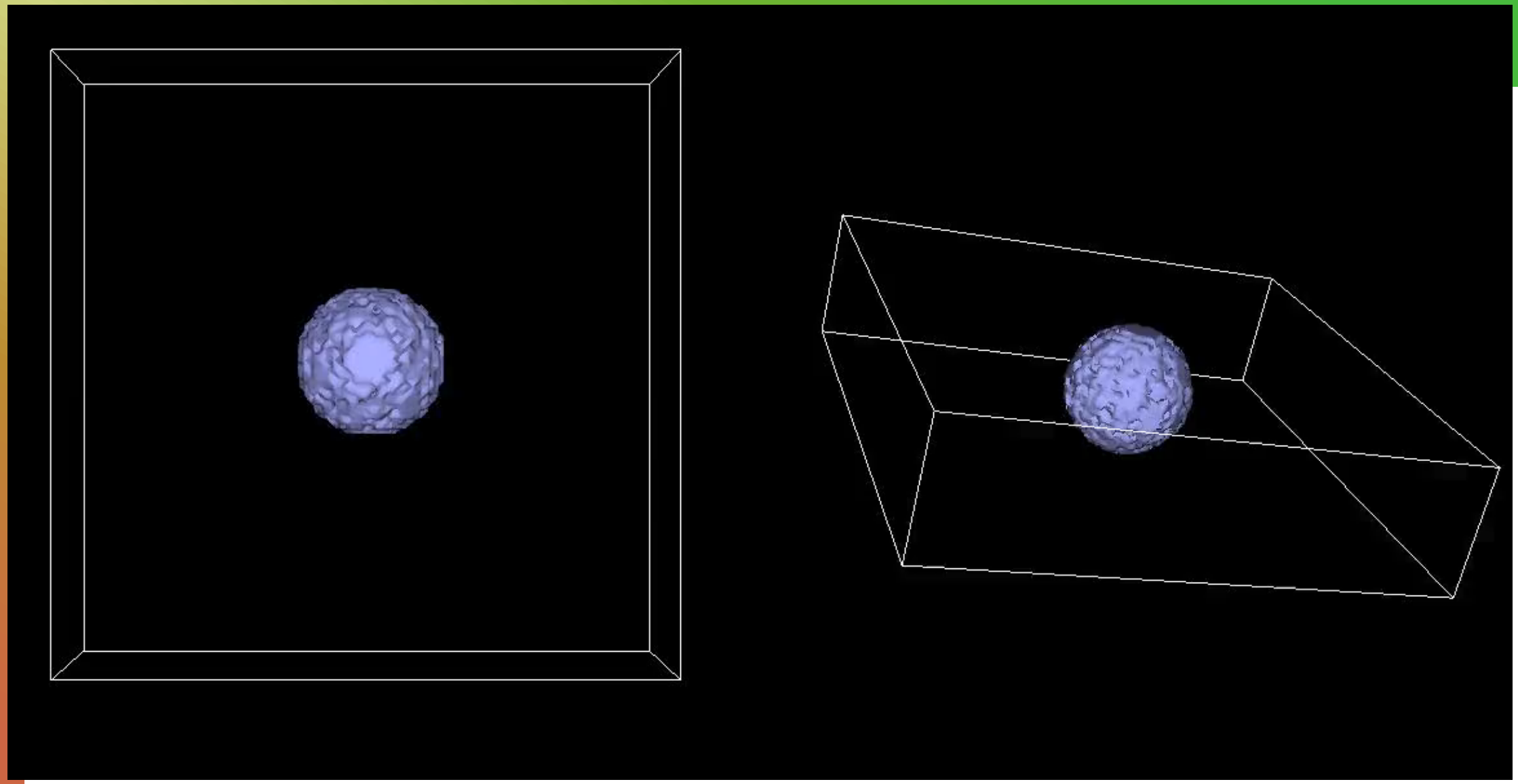
1) F-actin favors the overwriting of medium lattice sites (**black**) by lamellipodium (**green**) lattice sites
2) The volume constraint of the cell compartments backpropagates the lamellipodium extension and causes the cell to displace
3) The cell acquires a polarization axis, which causes the cell to migrate persistently in the direction of polarization

Polarization axis



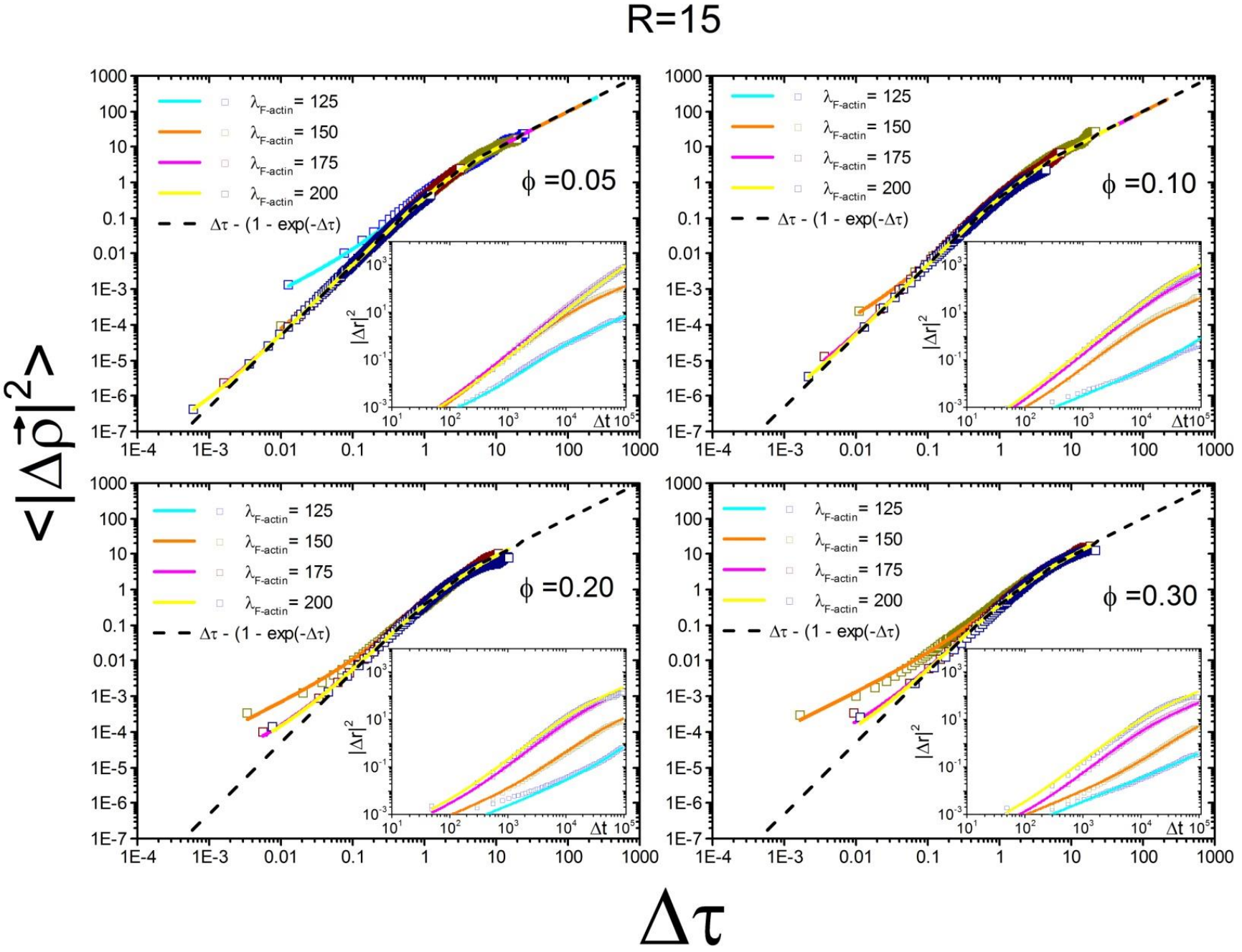


Schematic representation of the simulated cell by Ismael Fortuna

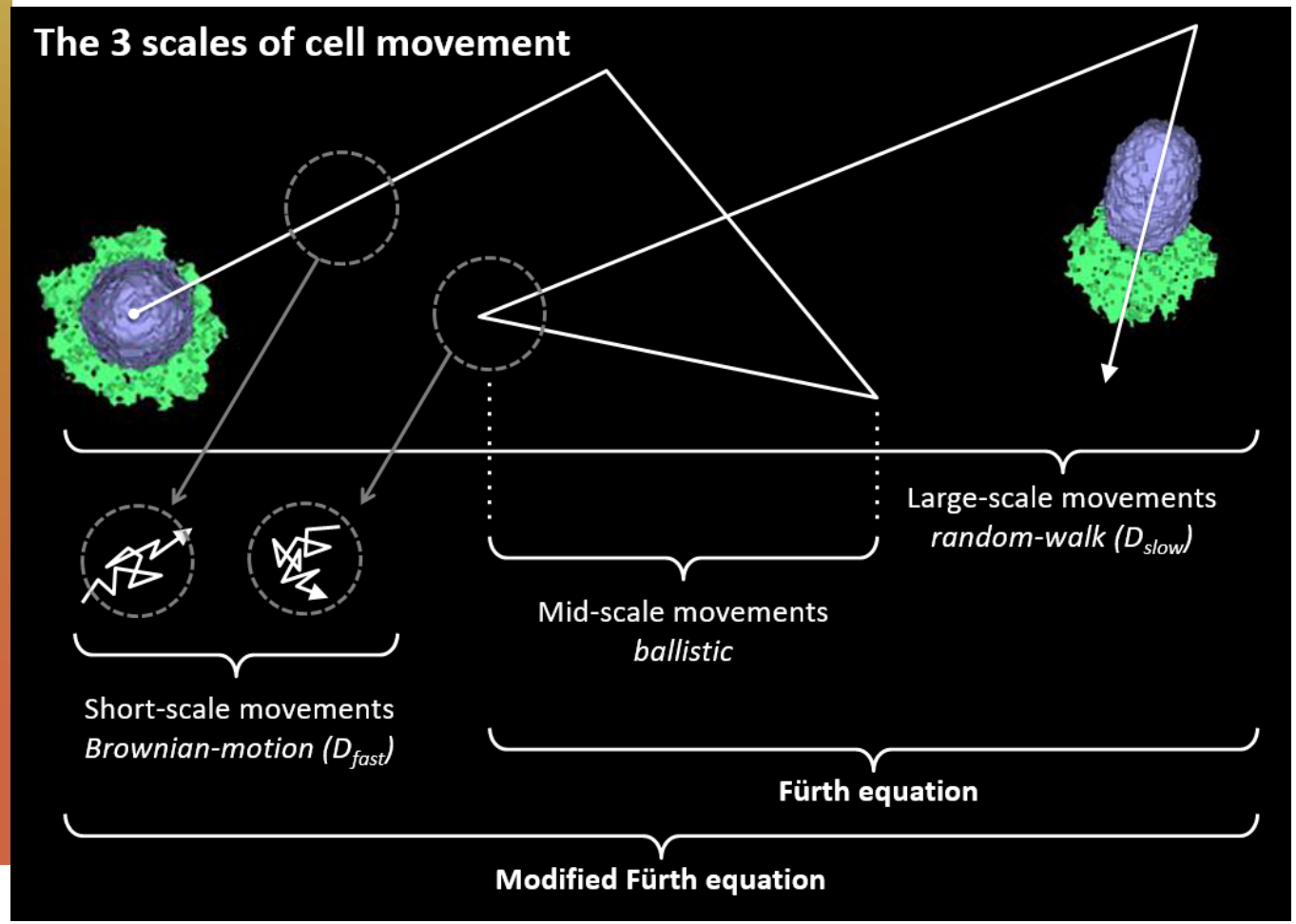


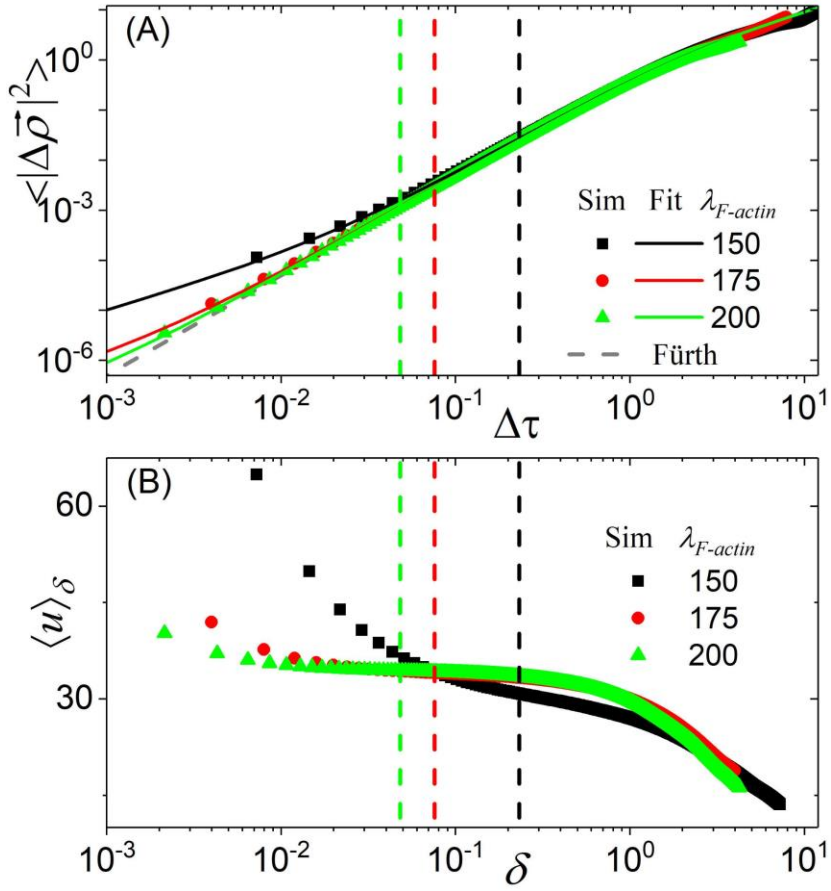
Simulations

Modified Furth Equation



Cell geometry and movement are correlated.
Are They?
How simulations may help.

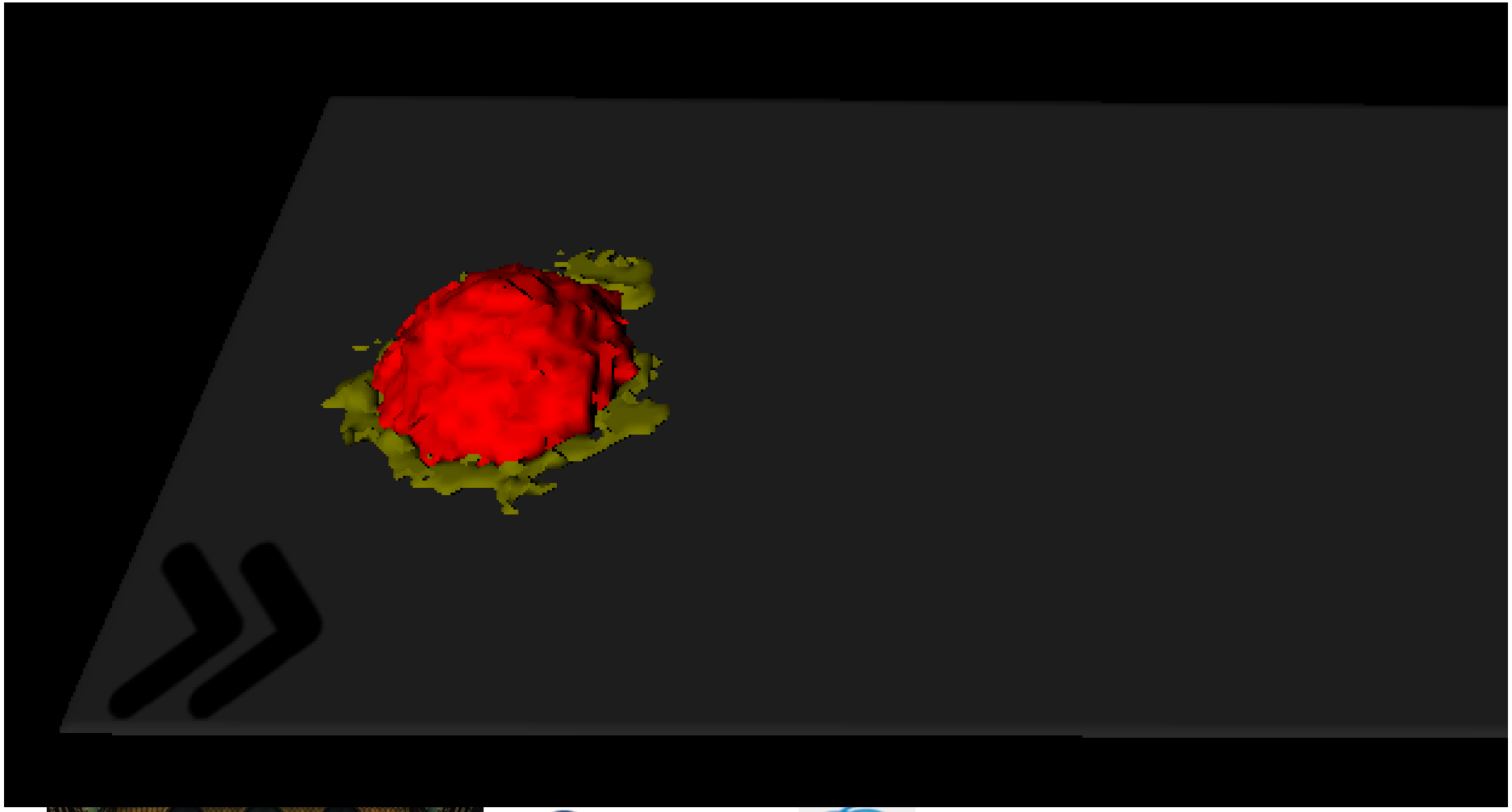




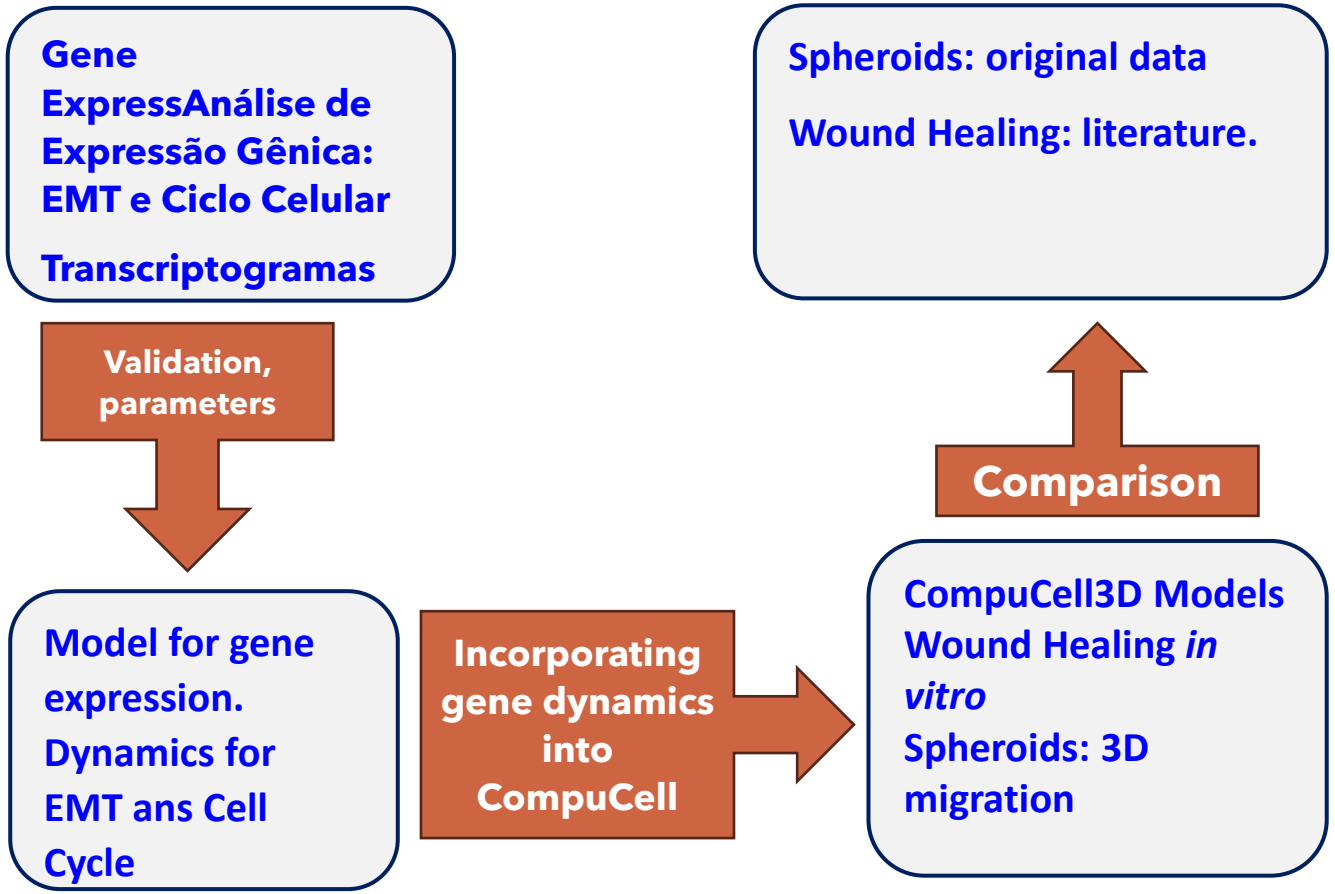
Thomas,...,RMCdA, Physica A, 550 (2020) 124493

Dal Castel,..., RMCdeA, 2023, in preparation

Chemotaxis



BACK to EMT


Gene ExpressAnálise de Expressão Gênica: EMT e Ciclo Celular
Transcriptogramas
Validation, parameters
Model for gene expression. Dynamics for EMT ans Cell Cycle
Incorporating gene dynamics into CompuCell
CompuCell3D Models Wound Healing *in vitro* Spheroids: 3D migration
Comparison
Spheroids: original data
Wound Healing: literature.

Regulatory gene networks and EMT

- Cell life is a manifestation of biochemical reaction involving many thousands of proteins, RNAs and metabolites.
- Non-linear reactions, interactions with cell invronment.
- Feed back loops
- Many attractors. Stable phenotypes associated with attractors.
- External stimulii may triger the transition between attractors
- EMT is such a case.(?)

Tripathi, Kessler, Levine
PRL,125, 088101 (2020); PNAS 120, e2216109120 (2023)

Biological networks are minimally frustrated

+ Simple models work;

+ Different models work.

+ There are Boolean models.

Tripathi, Kessler, Levine
PRL,125, 088101 (2020); PNAS 120, e2216109120

Inspired by spin systems!

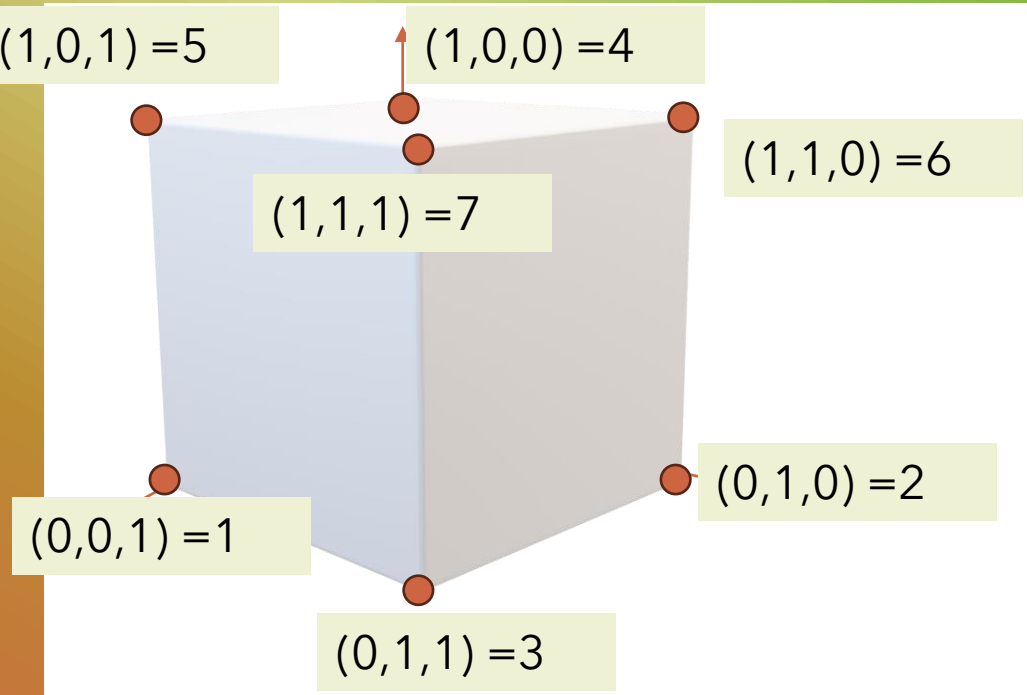
$$s_i(t+1) = \begin{cases} +1 & \sum_j J_{ij} s_j > 0 \\ -1 & \text{if} \quad \sum_j J_{ij} s_j < 0 \\ s_i(t) & \sum_j J_{ij} s_j = 0. \end{cases} \qquad (1)$$

Random networks: J_{ij} may assume -1,0,1 and are randomly chosen.
Comparison with biological systems with the same connections.

.

Stable states in biological networks have basins large basins of attraction and the stable states are minimally frustrated.

Information Space dynamics



De Almeida, Espinosa, Idiart
PRE **74**, 041912 2006

$$a(t) = \sum_{\sigma=0}^{2^M-1} y(\sigma,t),$$

$$\langle \tilde{S}_i(t) \rangle a(t) = \sum_{\sigma=0}^{2^M-1} y(\sigma,t)\sigma_i,$$

$$\langle \tilde{S}_i(t)\tilde{S}_j(t) \rangle a(t) = \sum_{\sigma=0}^{2^M-1} y(\sigma,t)\sigma_i\sigma_j,$$

$$\vdots$$

$$\langle \tilde{S}_1(t)\tilde{S}_2(t)\cdots\tilde{S}_M(t) \rangle a(t) = \sum_{\sigma=0}^{2^M-1} y(\sigma,t)\sigma_1\sigma_2\cdots\sigma_M, \quad (2)$$

$$\sigma = 0, 1, 2, \ldots, 2^M - 1$$

$y(\sigma, t)$ Intensidade de expressão da info σ

STATISTICAL MECHANICS FOR COMPLEXITY
A CELEBRATION OF THE 80TH BIRTHDAY OF CONSTANTINO TSALLIS
RIO DE JANEIRO, 6 TO 10 NOVEMBER 2023

CNPq CAPES

Lemke and de Almeida, 2004. Physica A 340, 309.

A dinâmica

$$y(\sigma,t+1) = [1 - y(\sigma,t)]y(\sigma,t)\lambda(\sigma,t),$$

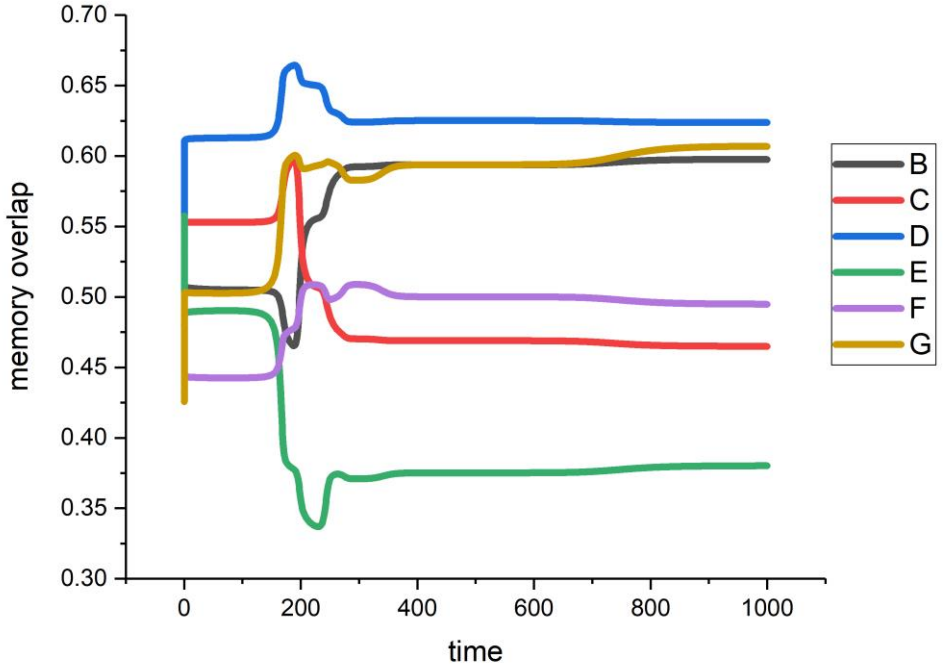
where

$$\lambda(\sigma,t) = x(\sigma) + \frac{\sum_{\sigma'} z(\sigma,\sigma')y(\sigma',t)}{\sum y(\sigma',t)}.$$

$$x(\sigma) = k_v + (k_m - k_v)\sum_{\mu=1}^{P} \delta(\sigma,\sigma^{\mu}),$$

.....

$$z(\sigma,\sigma') = z\delta(\sigma',\sigma^{(i)}),$$



Deshmukh et al. PNAS118, e2102050118 (2021)

Harvesting information from cells

- Single cell RNASeq for EMT➔ data on gene expression.
- EMT induction by TGFbeta. Measurements at t=0, t=1day and t=8 days.
- Results: there are diferente trajectories.

  There are transiente, hybrid states

  Different cells presente different transition rates.

Noise in experimental measurements may represent na issue.

Proposed models do not handle well the dependence with the stimulus application time.

Our proposal: Transcriptograms
Information space dynamics.

Transcriptogramas

Rybarczyk-Filho,..., RMCdeA, Nucleic Acids Research, 2011, Vol. 39 3005–3016
Morais, de Almeida, Dalmolin, Bioinformatics, 2019, 1–2
de Almeida et al. Human Genomics (2016) 10:37

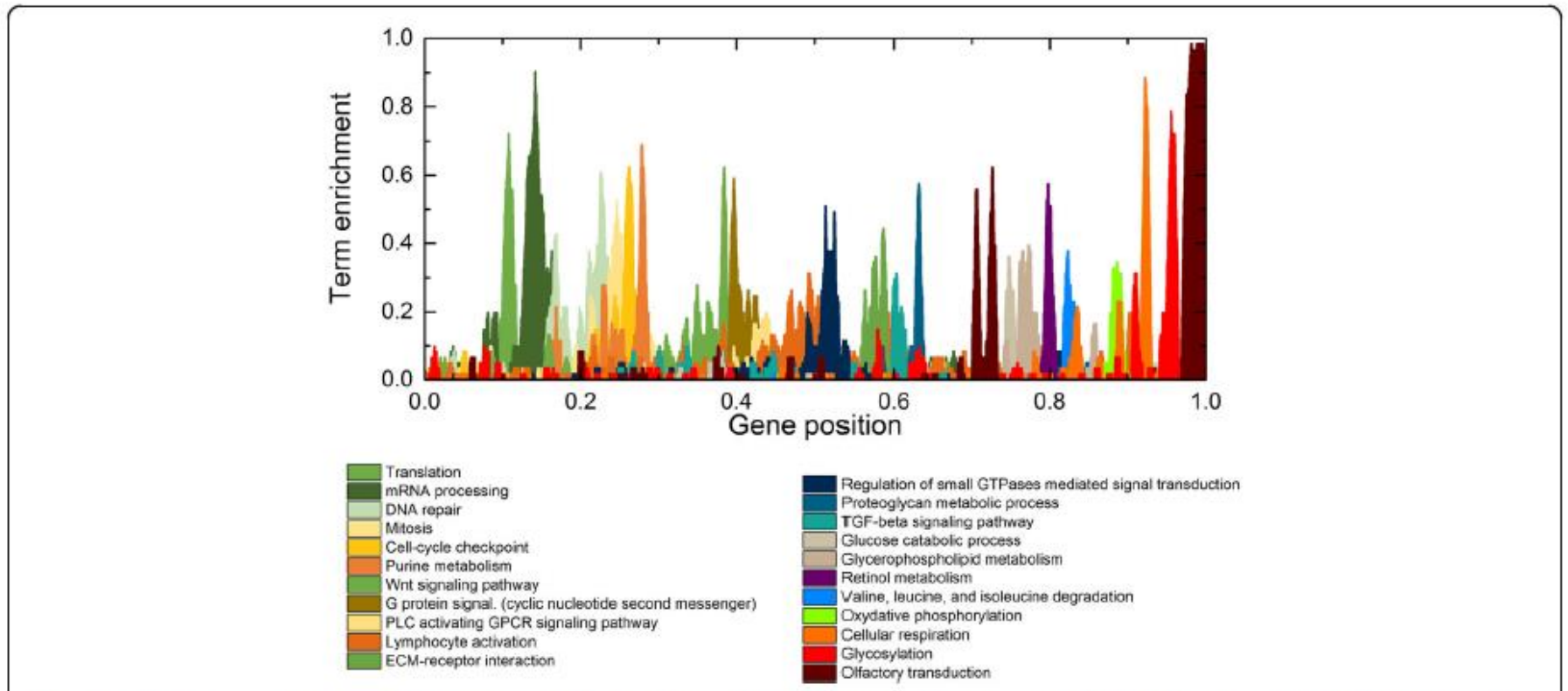
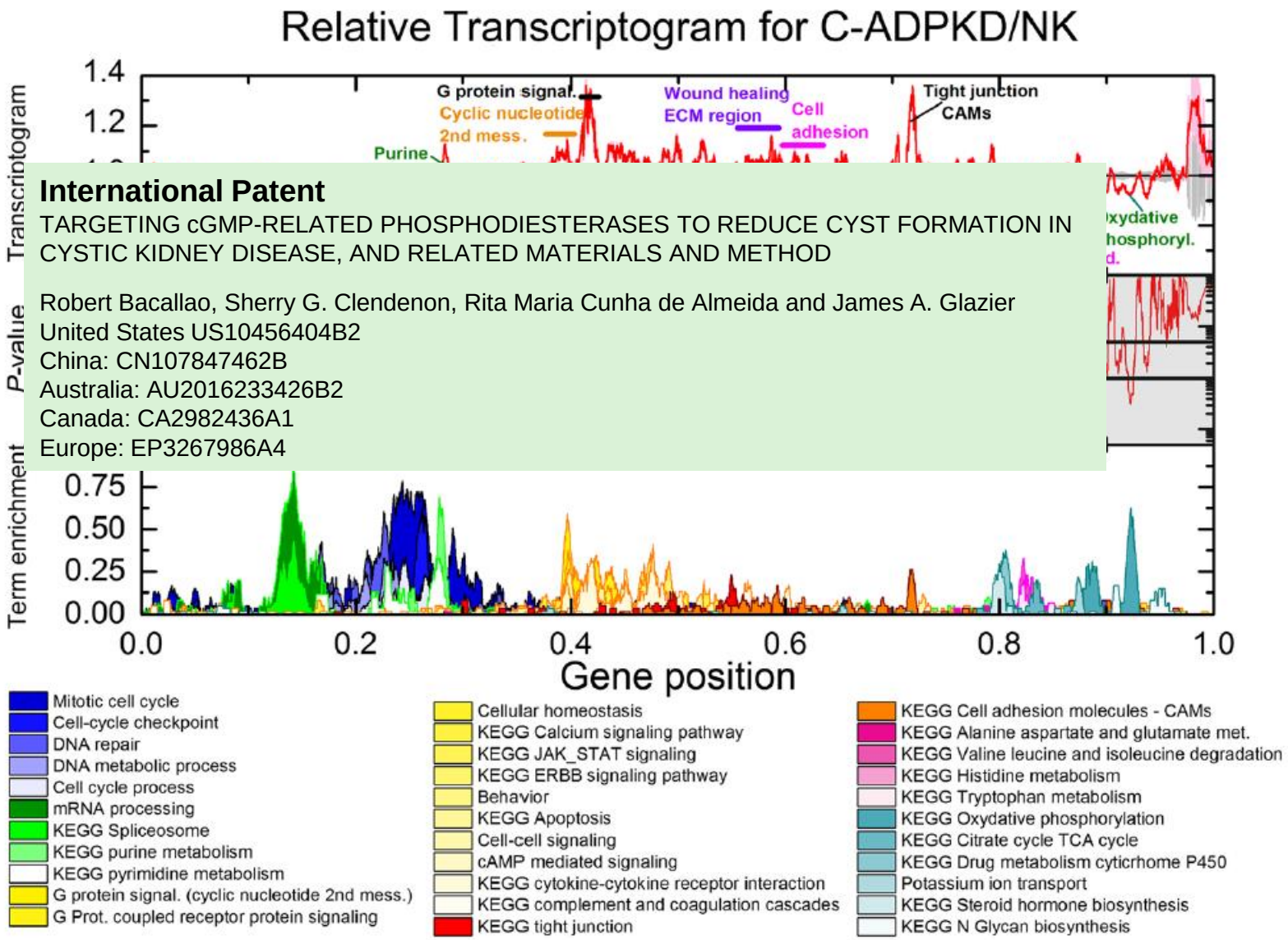


Fig. 3 Term enrichment map showing the correspondence between the ordered gene list and major biological terms and pathways. The *x*-axis indicates the relative position in the ordered list of 9684 genes. The colored profiles give the density distributions within the list of specific GO terms or KEGG pathways. A term enrichment value of 1 on the *y*-axis indicates that all genes in an interval of radius $r = 30$ participate in a given GO term or KEGG pathway. *Peaks* mark regions enriched with genes related to the term or pathway indicated in the legend. The legend orders the terms/pathways from left to right



International Patent

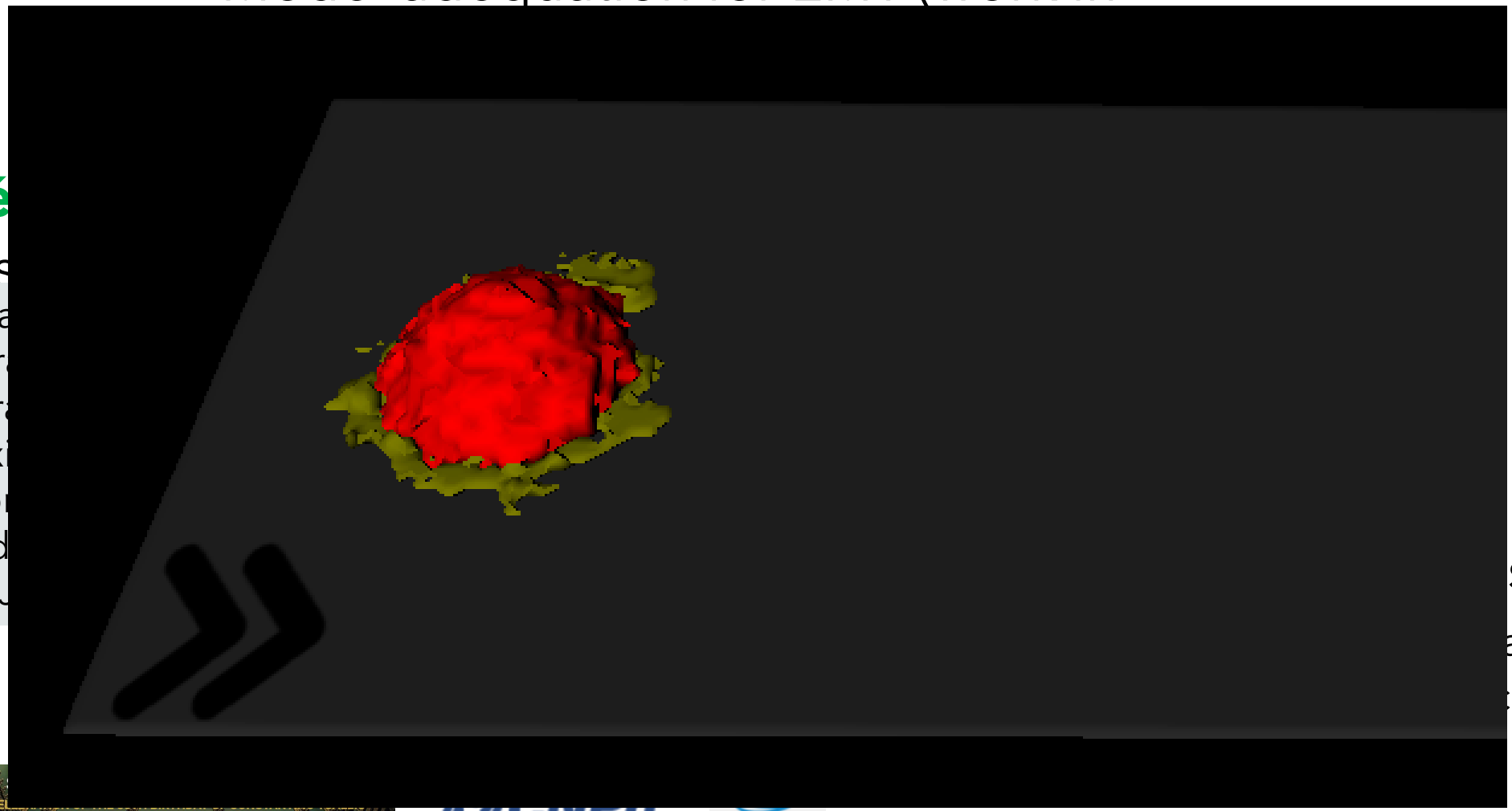
TARGETING cGMP-RELATED PHOSPHODIESTERASES TO REDUCE CYST FORMATION IN CYSTIC KIDNEY DISEASE, AND RELATED MATERIALS AND METHOD

Robert Bacallao, Sherry G. Clendenon, Rita Maria Cunha de Almeida and James A. Glazier
United States US10456404B2
China: CN107847462B
Australia: AU2016233426B2
Canada: CA2982436A1
Europe: EP3267986A4

The project

Metabolic pathways and EMT

✓ Model adequation for EMT (work in



Epité

✓ Pas

Mesenchymla
Isolated migr
✓ Flat substr
✓ Chemotaxi
✓ Polarizatio
• Shape and
Yi J

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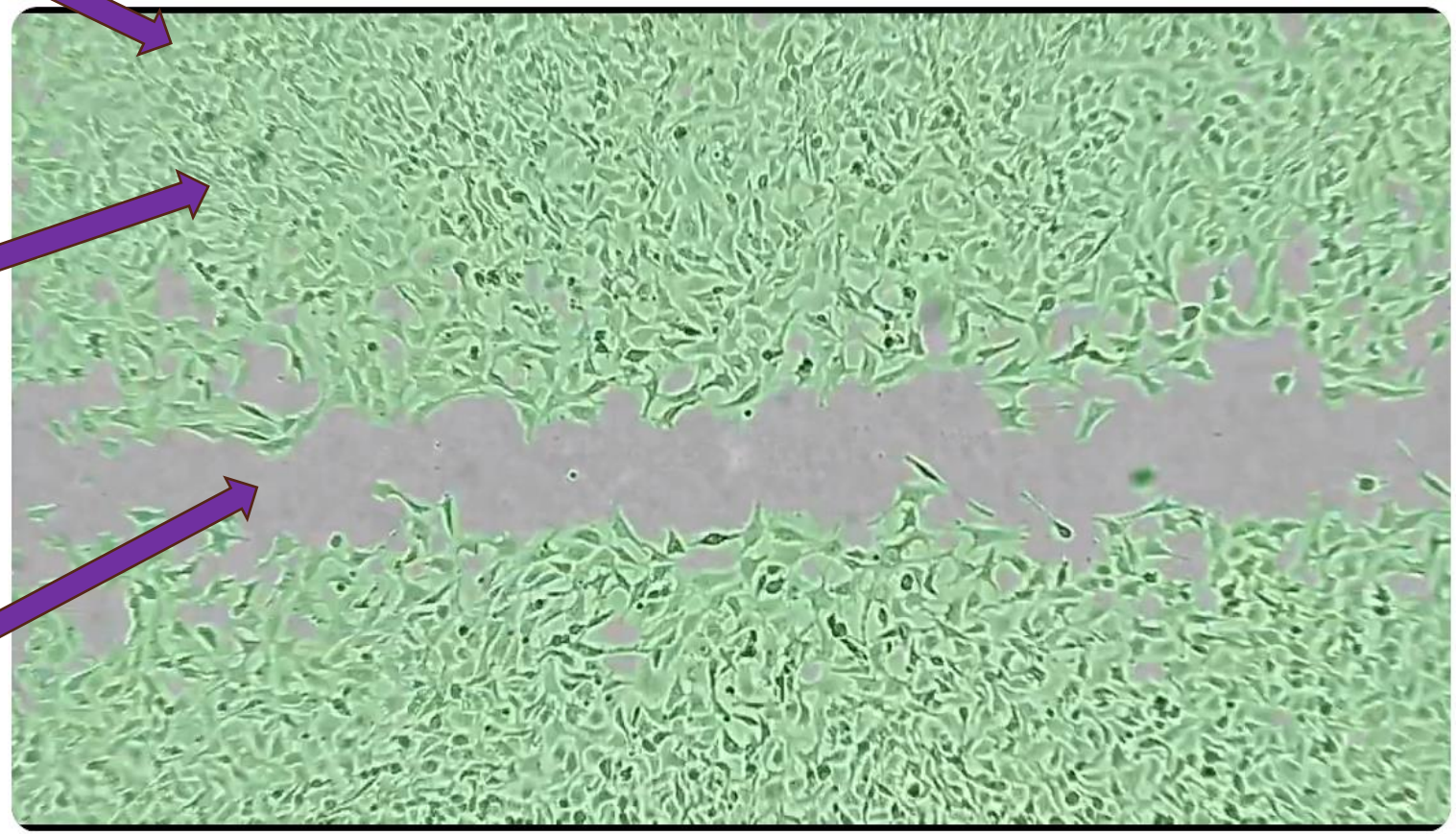
CAPES

Active solids: epithelium

Phenotype transition

Mesenchymal migration



Same cellular model

wound healing assay - Pesquisa Google

CNPq
CAPES

Vision and potentiale possibilidades

+ Digital twins (precision, personalized medicine)
+ Therapy and drugs
+ Tissue engineering

Thank you!

The computational model: Physics

$$E_{interface} = \sum_{\vec{r}} \sum_{\vec{v}(\vec{r})} J\left(\sigma(\vec{r}), C(\vec{r}); \sigma(\vec{v}), C(\vec{v})\right),$$

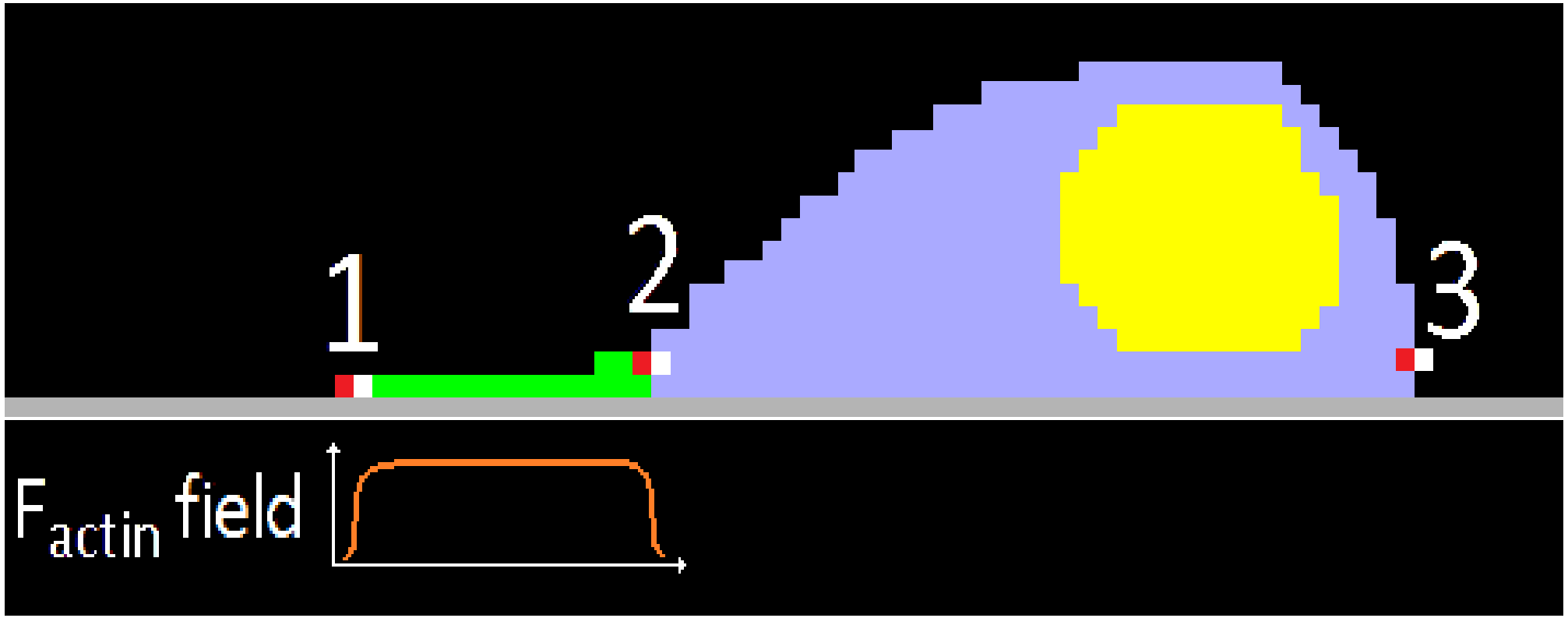
$$E_{target\ volume} = \sum_{C=1}^{3} \lambda_C \left(V_C - V_C^{target}\right)^2,$$

$$E = E_{interface} + E_{target\ volume}$$

$$\Delta E_{F-actin} = \lambda_{F-actin}[A(\vec{v}) - A(\vec{r})]\ \delta(C(\vec{r}) - 3)\ \delta(\sigma(\vec{v}) - \text{medium}),$$

$$\frac{\partial A(\vec{r}, t)}{\partial t} = D_F \nabla^2 A(\vec{r}, t) + k_{source} \delta\left(C(x, y, 1) - 3\right) - k_{decay}\ A(\vec{r}, t),$$

Células mesenquimais: Cellular Potts model



Fortuna, ..., RMCdeA, Biophysical Journal, 118, p 2801, 2020
https://doi.org/10.1016/j.bpj.2020.04.024

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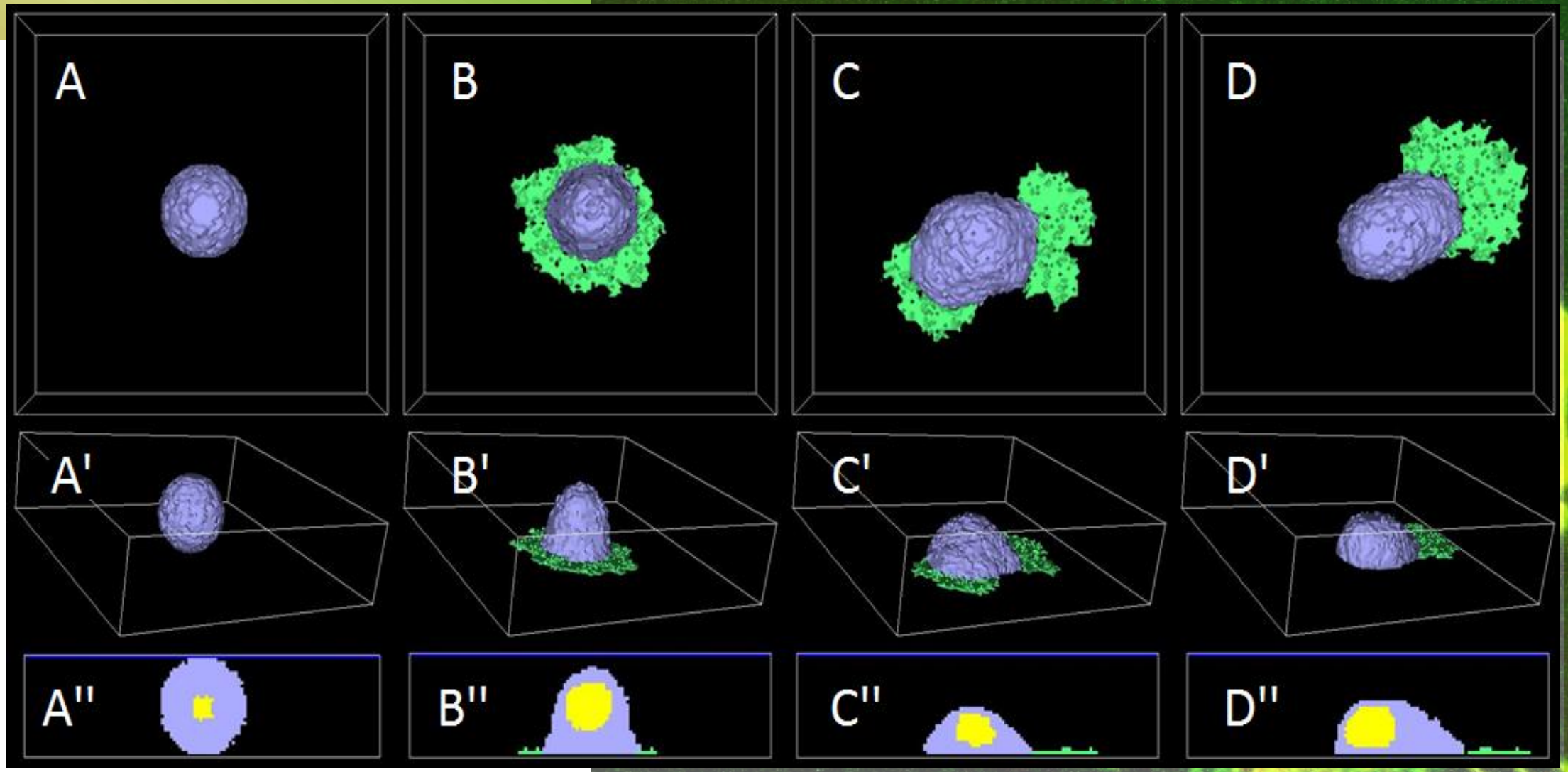
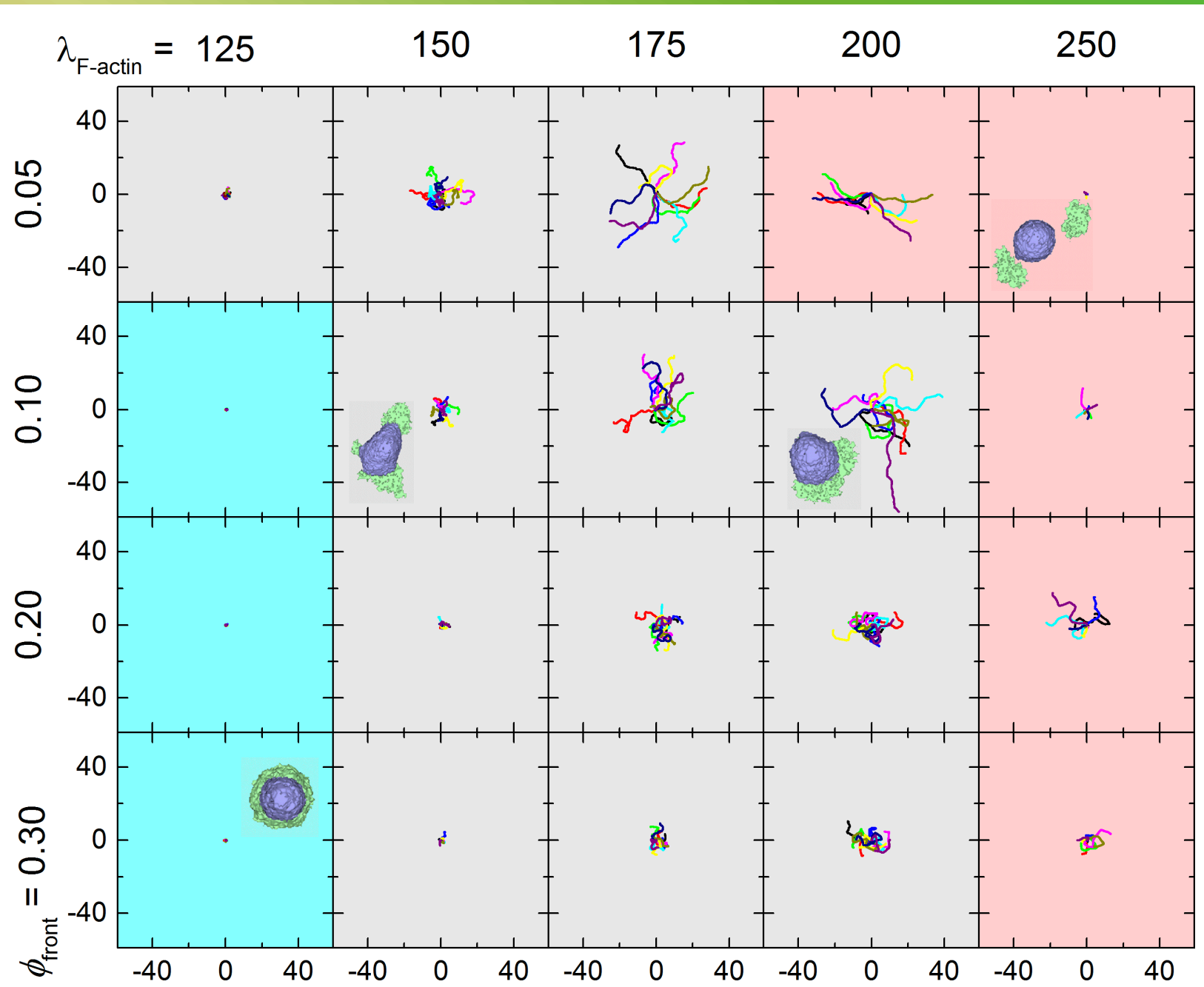
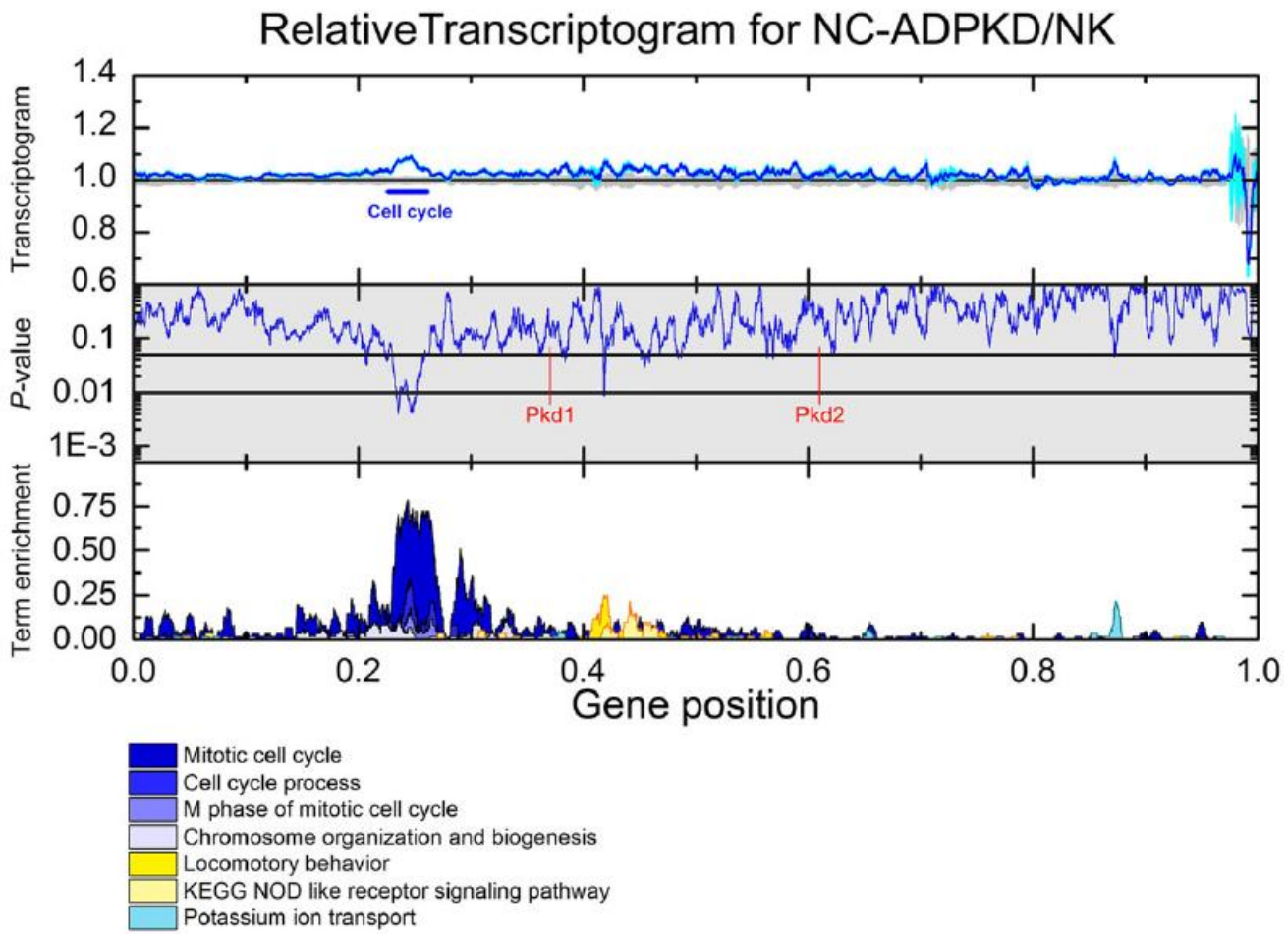
CAPES



Fortuna,...RMCdA., Biophysical J. 118, 2801-2815, 2020

Simulation Phenotypes




RelativeTranscriptogram for NC-ADPKD/NK
Transcriptogram
1.4
1.2
1.0
0.8
0.6
Cell cycle
P-value
0.1
0.01
1E-3
Pkd1
Pkd2
Term enrichment
0.75
0.50
0.25
0.00
0.0
0.2
0.4
0.6
0.8
1.0
Gene position
Mitotic cell cycle
Cell cycle process
M phase of mitotic cell cycle
Chromosome organization and biogenesis
Locomotory behavior
KEGG NOD like receptor signaling pathway
Potassium ion transport

EMT: multiscale, multi-organs, and cellular environment.

+ Cell biochemical alterations;
+ Secretion and reception of molecules;
+ Transport through blood stream.
+ Mechanical interactions (cell-cell adhesions, Cell-ECM adhesions)
+ Quantitative simulations aiming at personal, precision medicine.